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ARTICLE TYPE

A novel, efficient synthesis of *N*-aryl pyrroles via reaction of 1-boronodienes with arylnitroso compounds.

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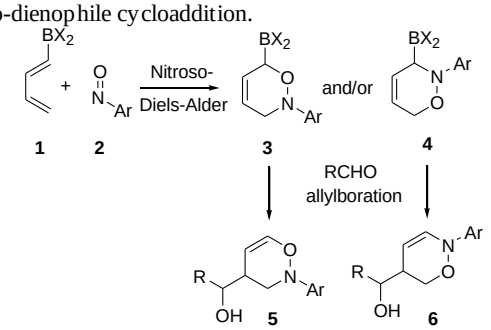
Abstract A one-pot hetero-Diels-Alder/ring contraction cascade is presented from the reaction of 1-boronodienes and arylnitroso derivatives to derive *N*-arylpyrroles in moderate to good yields (up to 82%). Experimental results and B3LYP calculations suggest that pyrrole formation proceeds *via* a 3,6-dihydro-1,2-oxazine followed by a novel boryl rearrangement and intramolecular aza-boryl to aldehyde addition-elimination sequence.

The wide ranging biological activity associated with pyrroles and particularly *N*-aryl pyrroles[1] makes them a popular target for the development of novel synthetic approaches, including multi-component assembly.[2] This communication reports a new and unexpected *N*-aryl pyrrole synthesis resulting from the reaction of an arylnitroso compound with a 1-boronodiene, revealing interesting mechanistic questions.

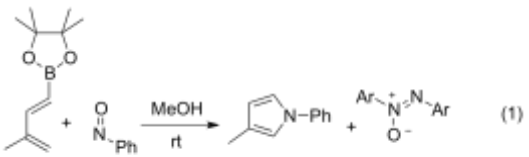
The reaction of nitroso compounds with dienes is well known,[3] deriving 3,6-dihydro-1,2-oxazines, which have a number of uses, including as bioactives and in synthetic applications.[4] As part of a programme to examine the potential of nitroso-dienophiles and 1-boronodienes[5] for the cascade construction of novel structures,[6] we examined the reaction of dienes **1** with arylnitroso compounds **2** with the expectation of obtaining the oxazines **3** and/or **4** from which cascade reactions could be carried out to access allylic alcohols **5** and/or **6** (Scheme 1).

Scheme 1. Proposed cascade process initiated by a boronodiene-nitroso-dienophile cycloaddition.



1 2 3 4 5 6

However, instead of cycloadducts of type **3** and/or **4** being observed, the unexpected *N*-phenylpyrrole **8** was identified (Eqn. 1) from the reaction of boronate ester **7** with nitrosobenzene. This prompted a more detailed investigation of this novel and intriguing process, and, in this communication, we report these preliminary studies.



7 8 9

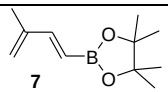
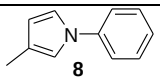
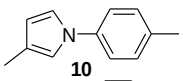
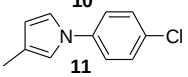
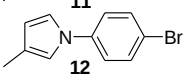
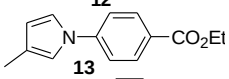
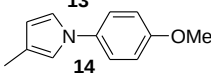
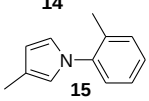
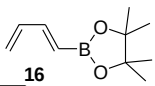
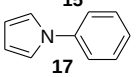
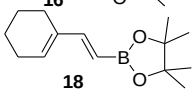
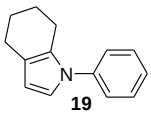
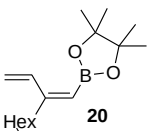
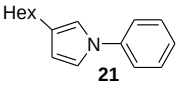
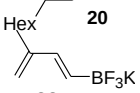
When this reaction (Eqn. 1) was repeated and followed *in situ* by ^{1}H NMR, no cycloadduct (of either type **3** or **4**) could be observed; only **8** and **9** were identified from the product mixture, together with starting materials. After 5 h, the reaction was complete and the pyrrole **8** could be isolated in up to 82% yield (Entry 3, Table 1). Further studies were therefore conducted to see if this surprising result is general.

Indeed, as shown in Table 1, different arylnitroso compounds do undergo this conversion with borylated dienes to provide the corresponding *N*-aryl pyrroles (Table 1). Yields were moderate to good and the reaction could be conducted in either methanol or DCM (see Entries 1, 2, Table 1) without an obvious solvent effect. A slightly higher yield appears to result from an excess of the arylnitroso compound (compare Entries 3 and 1, Table 1) and hence, 2.5 equivalents of arylnitroso compound was used for most of the reactions. Surprisingly, no significant influence was observed on either the nature or location of the aromatic ring substituent; major electronic effects were not apparent and yields for pyrroles **10**-**15** varied from 52 to 82% (Entries 4-9, Table 1).

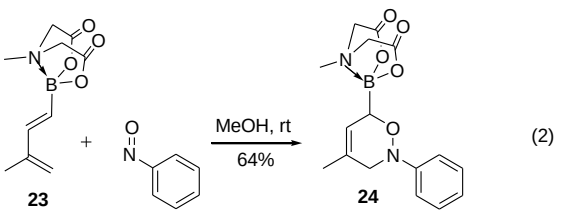
The less accessible diene **16** reacted with nitrosobenzene to give the corresponding pyrrole **17** in 78% yield. However, with a more sterically hindered diene **18**, there was a significant decrease of yield (16% for the pyrrole **19**) even after an extended reaction time (Entry 11, Table 1). Changing the dienylboronate geometry to (*Z*) as in compound **20** also had a detrimental effect upon the reaction, with adduct **21** only being isolated in 34% yield, after 16 h (Entry 12, Table 1). Interestingly, this reaction can be also carried out using a trifluoroborylated diene **22**, deriving the pyrroles **10**, **14** and **15** with slightly improved yields (Entries 13-15, Table 1) compared to the pinacol ester variants. With these reactions exemplified, we examined similar reactions using both *t*-butylnitroso and acylnitroso[7] with diene **7**, yet neither gave nitroso-Diels-Alder adducts.

Interesting results were obtained when MIDA and diethanolamine dienylboronates were examined with nitroso benzene, which might well reflect upon the mechanism (Eqns. 2-4). Using MIDA boronate **23** modifies the reactivity of the adjacent unsaturated moiety,[9] hence providing the stable [4+2] cycloadduct **24** in 64% yield; the regiochemistry being assigned by NOESY NMR. (correlation between the *o*-phenyl H's and one of NCH's on the oxazine ring).

Table 1. Arylnitroso to *N*-aryl pyrrole conversions by reaction with dienyl boronates.

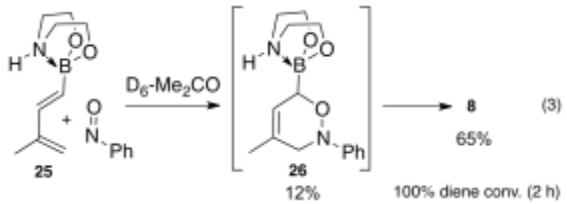
Entry	Diene[a]	Nitroso	Product	Conditions	Yield (%)[b]
1	 **7**	Ph-NO	 **8**	ArNO 1.5 equiv., MeOH, RT, 5 h	67
2	**7**	Ph-NO	**8**	ArNO 1.5 equiv., CH_2Cl_2, RT, 48 h	61
3	**7**	Ph-NO	**8**	ArNO 2.5 equiv., MeOH, RT, 5 h	82
4	**7**	4-Me-C_6H_4-NO	 **10**	"	60
5	**7**	4-Cl-C_6H_4-NO	 **11**	"	68
6	**7**	4-Br-C_6H_4-NO	 **12**	"	65
7	**7**	4-EtO_2C-C_6H_4-NO	 **13**	"	57
8	**7**	4-MeO-C_6H_4-NO	 **14**	"	71
9	**7**	2-Me-C_6H_4-NO	 **15**	"	52
10	 **16**	Ph-NO	 **17**	"	78
11	 **18**	Ph-NO	 **19**	ArNO 2.5 equiv., MeOH, RT, 16 h	16 .
12	 **20**	Ph-NO	 **21**	ArNO 2.5 equiv., MeOH, RT, 16 h	34
13	 **22**	4-Me-C_6H_4-NO	**10**	ArNO 2.5 equiv., MeOH, RT, 5 h	66
14	**22**	4-MeO-C_6H_4-NO	**14**	"	77
15	**22**	2-Me-C_6H_4-NO	**15**	"	69

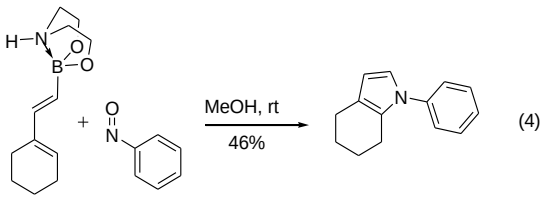
[a]For diene synthesis, see ref 8. [b]Yields are isolated yields after silica gel chromatography. Lower yields tend to reflect the difficulty of separating azo and azo-oxide by-products from the pyrroles; all conversions were high (with the exception Entry 11, which is a slow and less efficient reaction).



23 **24** (2)

Using the diethanolamine ester **25** (Eqn. 3) and following the reaction *in situ* by ^{1}H NMR (1.5 equiv. of PhNO), the cycloadduct **26** could be identified by comparison of its ^{1}H NMR with those of **24**. After 2 h, all diene was consumed, the boronated 1,2-oxazine had disappeared and pyrrole **8** (with small amounts of azoxybenzene **9** and 12% cycloadduct **26**) were detected, which suggests that the reaction is faster with a diethanolamine ester (50% conversion after 5 min at rt *vs*. 5 h for total conversion of the pinacol ester, Table 1, Entry 2). This observation is also reinforced by the reaction of diene **27**[11] (Eqn. 4) which, in 2 h, provided a 48% yield of pyrrole **19** (*c.f.* 16% in 16 h, Entry 11, Table 1). The observation of the boronated 1,2-oxazine **26** shows that in this case, pyrrole formation is preceded by a regioselective nitroso-Diels-Alder reaction, which we therefore presume extends to all the other examples shown in Table 1. It is also noteworthy that no pyrrole formation was observed if the cycloadduct is stable towards hydrolysis as it is the case for the MIDA derivatives (see Eqn. 2). Hence, it seems to be the case that tricoordinated sp^2 boron species are required for ring contraction from the oxazine to the pyrrole to take place. Finally, it appears that the arylnitroso is not required as a stoichiometric oxidant to effect pyrrole formation, and hence, a nitroso-based oxidation of the B-C bond of the oxazine might be ruled out as being involved in the ring contraction-pyrrole formation.

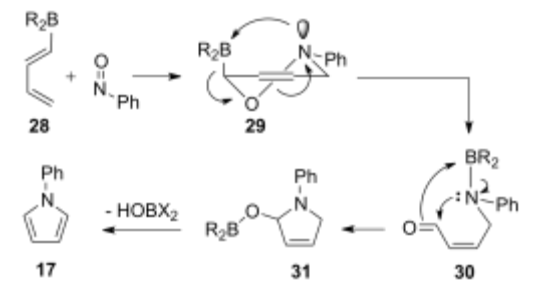




27 **19**

These results raise the obvious question as to the reaction mechanism. Although it is known that 3,6-dihydro-1,2-oxazines can be directly or indirectly converted to pyrroles, the conditions employed here (spontaneous ring contraction) are clearly quite different since this transformation mostly requires several steps,[12] specific substituents,[13] photolysis,[14] high temperature,[15] samarium diiodide,[16] oxidants,[17] basic or acid reagents.[18] For this case, we propose that the pyrrole formation proceeds (Scheme 2) through the Diels-Alder reaction of the boronodiene **28** to give **29**, followed by a boryl rearrangement (to give **30**), intramolecular aza-boryl to aldehyde addition (to give **31**) and borate elimination (to give **17**). This is supported by intrinsic reaction coordinate pathways of model geometries related to compounds shown in Scheme 2 computed at B3LYP/6-31G* (see ESI). All steps are computed to be exothermic thus supporting the proposed cascade process. In the initial Diels-Alder reaction step where four different pathways were determined, the lowest transition state (TS) barrier was found to be only 8.8 kcalmol^{-1}.

Scheme 2. Proposed mechanism for the reaction of boronodienes arylnitroso compounds to give pyrroles.



In conclusion, we report a novel approach to *N*-aryl pyrroles which we believe proceeds through a [4+2]-cycloaddition/ring contraction cascade process from arylnitroso compounds and 1-boronodiene. This reaction reveals interesting mechanistic features that are in agreement with similar behaviour previously observed with related five-membered ring heterocycles.[19] Further investigations to confirm the proposed rearrangement mechanism that derives the pyrrole products, its generality and the influence of the boron substituents are currently underway in our laboratories.

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Notes and references

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[†]Electronic Supplementary Information (ESI) available: Experimental details, characterisation data, ^{1}H and ^{13}C NMR spectra. See

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